REMARKS

Claims 1-2, 14-15, 23-26 and 38-39 were previously pending in this application. Claims 3-7, 9, 17, 20, 30-31 and 34-35 have been withdrawn as a result of the restriction requirement. As a result claims 1-2, 14-15, 23-26 and 38-39 are pending for examination with claims 1 and 15 being independent claims. No new matter has been added.

Specification

Applicants have amended the paragraph on page 24, beginning at line 22 to correct a typographical error. The letter C was inadvertently included at the end of the amino acid sequence of SEQ ID NO:3. The sequence is correctly described in the specification as filed as including residues 496-515 or TgAMA-1, which corresponds to the sequence: EFQSDRGARKKRPSDLMQEA. Applicants have amended the paragraph to remove the letter C that was erroneously included.

Applicants have also amended the specification to correct informalities by replacing line 1 on page 35, with the phrase: What is claimed is.

Sequence Listing

Applicants have amended the sequence included as SEQ ID NO:3 to reflect the correction of the typographical error in the specification described above. SEQ ID NO:3 in the sequence listing included the letter C, which is not part of the sequence of residues from 496-515 of TgAMA-1. Applicants have submitted a substitute sequence listing and computer readable form of the sequence listing to Mail Stop Sequence Listing and provide a paper copy of the sequence listing herewith. No new matter has been added.

Priority

The Examiner states on page 2 of paper 14 that that the provisional application 60/247,870 upon which priority is claimed fails to provide adequate support under 35 U.S.C. §112 for claims 1-2, 14-15, 23-26, 38 and 39 drawn to an isolated polypeptide SEQ ID NO:1 of this application. Applicants respectfully disagree with this conclusion and assert that SEQ ID NO:1 is the sequence of TgAMA-1 as was filed in the provisional application. The TgAMA-1

polypeptide is clearly identified in the specification of the provisional application at page 4, line 15 and the instant application at page 29, lines 23-24 as the sequence deposited in Genbank as accession number: AF010264. Applicants have attached a copy of the Genbank printout of the sequences herewith and submit that this sequence is identical to the sequence disclosed as TgAMA-1 (SEQ ID NO:1) in the instant application. Because the sequence identified as TgAMA-1 in the provisional application is the same sequence identified as TgAMA-1 and SEQ ID NO:1 in the instant application, Applicants assert that the provisional application 60/247,870 does provide adequate support under 35 U.S.C. 112 for claims 1-2, 14-15, 23-26, and 38-39.

Information Disclosure Statement

Applicants gratefully acknowledge the Examiner's signature on the Information Disclosure Statement submitted by Applicants on Feb. 25, 2002, paper number 3. Applicants note that a single reference, reference A2, was not acknowledged by the Examiner on the Form PTO-1449 submitted by Applicants. Applicants respectfully request clarification from the Examiner regarding this omission. If the omission was unintentional, Applicants respectfully request that the Examiner provide a copy of the Form PTO-1449 that includes the Examiner's initialing of reference A2.

Rejections Under 35 U.S.C. §112

Written Description

The Examiner rejected claims 1-2, 14-15, and 38-39 under 35 U.S.C. §112, first paragraph as lacking written description. Applicants respectfully traverse the rejection.

The basic requirement of the written description requirement is that the claimed invention must be described clearly enough to allow one of ordinary skill in the art to recognize that the inventors invented the claimed invention. *Vas-Cath v. Mahurkar* 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991); *Lockwood v. American Airlines, Inc.* 107 F.3d 1565, 41 USPQ2d 1961 (Fed. Cir. 1997); *In re Gosteli* 872 F.2d 1008, 10 USPQ 2d 1614 (Fed. Cir. 1989). The requirement is based on the knowledge of the skilled artisan in the particular art: the applicant must convey to one of ordinary skill in the art through the disclosure of the invention that the applicant was in possession of the claimed invention.

The claimed invention is, in part, a genus of polypeptides that are antigenic fragments of TgAMA-1 (SEQ ID NO:1). The claimed invention also relates in part to fusion proteins that include a polypeptide fragment of the invention, binding polypeptides that bind to a polypeptide fragment of the invention, and a vaccine composition comprising SEQ ID NO1, or a fragment or variant thereof.

As a basis for the conclusion that one of ordinary skill would not recognize that Applicants were in possession of the claimed invention at the time of filing, the Examiner suggests that the specification as filed does not disclose antigenic fragments of TgAMA-1 polypeptide. Applicants respectfully disagree with this conclusion and submit that the specification does describe the characteristics of antigenic fragments of TgAMA-1 (SEQ ID NO:1) and also discloses specific antigenic fragments of TgAMA-1 that are representative species of the claimed genus of polypeptides. One an antigenic fragment of TgAMA-1 is a polypeptide that includes amino acids 496-515 of TgAMA-1, which is disclosed in the specification at page 24, line 22. Another example of an antigenic fragment of TgAMA-1 (SEQ ID NO:1) is disclosed at page 4 line 25, with the statement that the extracellular domain of TgAMA-1 is useful as a vaccine, thus indicating to one or ordinary skill in the art that the extracellular domain is antigenic. The specification describes the transmenbrane domain of TgAMA-1 at page 29, line 31 as between residues 457 and 476. Thus, one of ordinary skill in the art would recognize from the specification that the extracellular domain of TgAMA-1 includes amino acids 1-465 of the TgAMA-1 polypeptide, and that this fragment of TgAMA-1 is antigenic. Applicants submit that not only are those of ordinary skill in the art provided with representative examples of antigenic fragments of TgAMA-1 (SEQ ID NO:1), the specification also provides a clear description of what constitutes a fragment of TgAMA-1 and how one of ordinary skill can routinely identify such fragments. Applicants respectfully submit that one of ordinary skill in the art would know that Applicants, having provided specific amino acid sequences of antigenic polypeptide fragments of TgAMA-1 (SEQ ID NO:1) and describing methods of identifying antigenic fragments of TgAMA-1 (SEQ ID NO:1, were in possession of the invention at the time of filing of the application.

The Examiner also suggests at page 4 of the Office Action that the specification does not disclose "fusion proteins comprising said fragments" of TgAMA-1 (SEQ ID NO:1). Applicants

respectfully submit that fusion proteins were well known and routinely made and used in the art at the time of filing and assert that the description on page 6, lines 23-30 of fusion proteins that include the TgAMA-1 polypeptide fragments of the invention, examples of which are provided in the specification as described above, is sufficient to lead one of ordinary skill in the art to conclude that Applicants were in possession of the claimed invention at the time of filing.

The Examiner indicates at page 4 of the Office Action that the specification does not disclose "vaccine compositions comprising said fragments or functionally active variant" of TgAMA-1 (SEQ ID NO:1). Applicants respectfully disagree with this conclusion. The specification at page 15, lines 15-16 clearly teaches the administration of TgAMA-1 polypeptides of the invention in the form of a vaccine. In addition, the specification indicates that TgAMA-1 polypeptides of the invention include variants, and the specification at page 6, line 5 through page 9, line 4 provides extensive description of functional variants of TgAMA-1 polypeptides of the invention. Applicants submit that the description of functional variants of TgAMA-1 and fragments thereof, provided in the specification as filed, would clearly indicate to one of ordinary skill in the art that Applicants were in possession of the claimed invention at the time of filing.

The Examiner additionally indicates at page 5 of the Office Action, that the specification does not describe "actual structure or other relevant identifying characteristics of each fragment having the claimed properties of the polypeptide, SEQ ID NO:1." Applicants respectfully disagree with this conclusion. The relevant identifying characteristics of each claimed fragment of SEQ ID NO:1 are: 1) the sequence has one or more residues fewer than SEQ ID NO:1 and 2) the polypeptide is antigenic. Applicants respectfully assert that these two features are clearly described in the specification as filed and the disclosure of these features, in conjunction with the extensive description in the specification as filed relating to the use of polypeptides with these features in fusion proteins and vaccine compositions would indicate to one of ordinary skill in the art that Applicants were in possession of the claimed invention at the time of filing.

Enablement

The Examiner has rejected claims 1-2, 14-15, and 38-39 under 35 U.S.C. §112, first paragraph as lacking enablement. Applicants respectfully traverse the rejection.

The Examiner states on page 6 of the Office Action, that the "specification fails to indicate the biological activity of said fragments of SEQ ID NO:1 . . . and further lacks any description of polypeptide SEQ ID NO:1, which acts as a vaccine." Applicants respectfully disagree with this conclusion and assert that the appropriate test for an enablement analysis is whether one of ordinary skill in the art would be required to use undue experimentation to practice the invention. Thus, requiring Applicants to have demonstrated a functional vaccine composition as of the time of filing the application is an inappropriate standard.

Applicants submit that a complete enablement evaluation necessitates the analysis of the so-called Wands factors as set forth in *In re Wands* 858 F.2d 731, 737, 740, 8 U.S.P.Q.2d 1400, 1404, 1407 (Fed. Cir. 1988). The Examiner appears to have considered some of the *Wands* factors, (although they were not described as such); however, all of the factors must be considered for a proper analysis, and a finding of nonenablement must be based on the evidence as a whole. Applicants submit that full consideration of each and all of the *Wands* factors, in view of the state of the art at the time of filing, leads one to the reasonable conclusion that practicing the invention would not require undue experimentation.

The Examiner appears to have considered the level of guidance provided in the specification as filed and asserts on page 6 of the Office Action that "the skilled artisan is provided no guidance to test, screen or make fragments of the polypeptide or the functionally active fragments of SEQ ID NO:1 using conventional technology which allow for a vaccine use in the specification." Applicants assert that the specification as filed does include the requisite teaching, to allow one of ordinary skill to make, identify, test, and use antigenic fragments of TgAMA-1 (SEQ ID NO:1) in the methods and compositions of the invention, for example at page 6, line 5 though page 11, line 18, and the Examples section.

Applicants submit that at page 8, lines 20-24, the specification provides a clear description of what constitutes a polypeptide that is a fragment of the TgAMA-1 polypeptide, as a polypeptide with one or more amino acids fewer than the polypeptide set forth as SEQ ID NO:1. In addition, the specification at Page 6, line 31 through page 7, line 12 teaches a method for determining the antigenicity of a fragment of TgAMA-1 (SEQ ID NO:1) by one of ordinary skill in the art. The model footpad test system was available at the time of filing to test the antigenicity of polypeptides. Additional methods are also provided in the specification that

allow one of ordinary skill in the art to utilize an identified antigenic fragment of TgAMA-1 (SEQ ID NO:1) in a vaccine composition. Page 19, line 18 through page 23, line 29 provide extensive detail regarding making, testing, and using polypeptides in a vaccine composition. For example, one can test an antigenic fragment of TgAMA-1 (SEQ ID NO:1) in an animal model of immunization, e.g. a mouse model of toxoplasmosis infection. Applicants assert that methods to make and test a vaccine comprising a fragment of TgAMA-1 (SEQ ID NO:1) would be considered routine among those of ordinary skill in the vaccine-related arts. Thus, Applicants submit that one of ordinary skill would be able to use routine methods to identify and use the antigenic fragments of TgAMA-1 (SEQ ID NO:1) of the invention without undue experimentation.

The Examiner has also apparently considered the predictability of the art, although perhaps using an excessively stringent standard. The Examiner asserts that polypeptide chemistry is unpredictable and suggests that the art teaches that "even a single amino acid change in a polypeptide leads to unpredictable changes in the biological activity of the polypeptide" (Office Action at page 7). Applicants assert that when provided with an amino acid sequence such as SEQ ID NO:1, one of ordinary skill in the art would be able to use routine methods available at the time of filing such as those cited at page 7, line 21, as taught in the PCT application of Stominger and Wucherpfennig (US/96/03182) along with descriptions provided on pages 6 through 11 of the specification to compare and predict potential epitopes and thus would be able to reliably identify, make, and test polypeptide fragments of TgAMA-1 (SEQ ID NO:1) as disclosed in the application without undue experimentation. Applicants submit that methods such as antigenic motif prediction, which were known in the art at the time of filing in 2000, would be used by one of ordinary skill in the art in conjunction with the teaching in the specification, thus obviating the assertions of unpredictability in the art presented by the Examiner.

The Examiner appears to have considered the level of knowledge in the art. The Examiner states that little is known about the AMA protein and its role as a vaccine composition and cites this as evidence of the state of the art. Applicants submit that the art of vaccine biology is the area of art in which the level of knowledge should be assessed, not simply the narrow area relating to vaccine production involving AMA protein. The state of vaccine technology is

applicable to vaccines based many different polypeptides and Applicants assert that methods routinely utilized in the vaccine arts in general are applicable to enablement of the claimed invention, not just methods relating to the AMA protein. Applicants submit that methods of making vaccines from polypeptides are routinely used by those of ordinary skill in the art, and the level of knowledge in the art is sufficient to enable the invention as claimed herein.

The Examiner does not appear to have considered the remaining *Wands* factors: 1) existence of working examples, 2) quantity of experimentation, 3) breadth of the claims, 4) the nature of the invention, and 5) the level of one of ordinary skill in the art. Applicants submit that none of these factors would weigh against a finding of enablement for the claimed invention. For example, very little experimentation is required to make, test and use fragments of TaGAMA-1 (SEQ ID NO:1) once the sequences of those polypeptides are taught as including antigenic polypeptides with one or more fewer amino acids than the full extent of SEQ ID NO:1, as was done in the instant application.

Applicants are uncertain of the relevance of the Examiner's suggestions at page 8 of the Office Action, that the specification "fails to teach even one of the claimed polynucleotide encoding polypeptides or fragments thereof" and "the specification fails to teach that the claimed polynucleotide encoding a polypeptide peptide or fragment or variant thereof are able to perform as a vaccine (i.e. protection, reduction in morbidity and/or mortality of disease) and the art does not recognize other similar nucleic acids as operative vaccines." Applicants respectfully submit that the claimed invention relates to polypeptide fragments of TgAMA-1 (SEQ ID NO:1) and requests clarification of the relevance of the Examiners comments regarding nucleic acid and vaccines.

Applicants maintain that adequate examples and guidance were provided in the specification as filed. As described above, Applicants provided extensive descriptions of fragments and variants of TgAMA-1 (SEQ ID NO:1) polypeptide (see, e.g., pages 6-11 and Examples), including specific sequences of fragments, methods to identify epitope motifs and fragments and variants, etc. Methods for testing the antigenic function of the fragments of polypeptides were well known at the time of filing and Applicants also included a specific foot pad test, with which one of ordinary skill in the art can determine antigenicity of fragments of

TgAMA-1 (SEQ ID NO:1) on page 6, line 31 through page 7, line12). These descriptions provide sufficient guidance to one of ordinary skill in the art at the time of filing (in 2000) to make and use the claimed antigenic fragments of TgAMA-1 (SEQ ID NO:1). With respect to the working examples *Wands* factor, the court in *Wright* stated that "Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright* at 1561 *citing In re Marzocchi* 439 F.2d 220, 223, 169 USPQ 367, 369 (C.C.P.A. 1971). Applicants have provided not only broad terminology which is readily understandable to one of ordinary skill in the art, but also illustrative examples of antigenic fragments and methods to identify, make, test, and use them in the claimed invention. Thus, the examples and guidance presented are not, by themselves, sufficient reasons to find undue experimentation.

The quantity of experimentation that would be required to practice the claimed invention is not excessive. Rather, the nature and quantity of such experimentation is completely routine in the relevant art. Selecting a polypeptide fragment of a larger polypeptide, assessing antigenic motifs and variants, and testing such a polypeptide, are standard experimental procedures in immunology and vaccine biology. For example, given the state of the art, one of ordinary skill in the art would only use routine experimentation to predict and generate a series of polypeptides and test them in cells and/or animal systems. Based on the results obtained, additional rounds of experimentation could focus on preferred molecules or variants having modified polypeptides as disclosed in the application. Such experimentation is routine as shown by the cited patents and numerous references relating to vaccine production that were publicly available at the time of filing of the application. Accordingly, any experimentation required would not be undue.

The claims are not excessively broad. Applicants have claimed polypeptide fragment compositions based on the disclosed full amino acid sequence of TgAMA-1 (SEQ ID NO:1), which are antigenic. The nature of the invention, which includes antigenic compositions, as well as vaccine compositions, is well known to one of ordinary skill in the art, as evidenced by the teaching in the art, including, but not limited to US Patent No:5,726,292, which issued in 1998 and discloses methods of making and using proteosome vaccines based on peptide sequences.

Applicants submit that the state of the prior art, along with the level of one of ordinary skill in the art, which is the final *Wands* factor, are crucial to any determination of undue

experimentation. In the *Wands* case, for example, the court's decision turned on the "high level of skill in the art at the time the application was filed", and that "all of the methods needed to practice the invention were known." *Wands* at 740, 8 USPQ2d at 1406. Applicants maintain that the same conclusions with respect to the state of the art and the level of skill in the art are true in the instant case, and therefore must weigh heavily in favor of a finding that undue experimentation is not required.

The level of skill in the art has an important effect on the amount of guidance which must be provided to enable the invention. As the court stated in *In re Howarth*, "[i]n exchange for the patent, [the applicant] must enable others to practice his invention. An inventor need not, however, explain every detail since he is speaking to those skilled in the art." *In re Howarth*, 654 F.2d 103, 105 (C.C.P.A. 1981). Thus the level of knowledge of one of ordinary skill in the art cannot be ignored in the *Wands* factor analysis. For the standard procedures contemplated in the application, the level of skill in the art is high. Applicants maintain that the person of skill in the art of vaccine biology would know how to prepare, test and use the claimed polypeptide fragment compositions.

In summary, a full analysis of the *Wands* factors favors a conclusion that only routine experimentation would be required of one of ordinary skill in the art to practice the claimed invention throughout its scope. Accordingly, Applicants respectfully request that the Examiner withdraw the rejections of claims 1-2, 14-15, and 38-39 made under 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §102

The Examiner rejected claim 1 under 35 U.S.C. §102(b) as being anticipated by Hehl et al. 1997, Accession number AF010264 and by Hehl et al. 1998, Accession number O15681. Applicants respectfully traverse the rejection.

To support a case for an anticipation rejection under 102(b), the reference must teach every claimed element of the invention. Applicants respectfully submit that claim 1 relates to antigenic fragments of TgAMA-1 (SEQ ID NO:1), and not the full TgAMA-1 polypeptide. The term "fragment" as used in relation to the polypeptides of the invention is defined at page 8, lines 21-22 of the specification as a polypeptide having one or more fewer amino acids than the

polypeptide set forth as SEQ ID NO:1. Thus, a fragment of TgAMA-1 (SEQ ID NO:1) is clearly a piece of TgAMA-1 (SEQ ID NO:1) and is not the full polypeptide sequence of TgAMA-1 (SEQ ID NO:1). Therefore, Applicants respectfully submit that the disclosures of the full-length 541 amino acid of TgAMA-1 in the Hehl references, which is referred to in the instant specification as SEQ ID NO:1, does not anticipate the claim to an antigenic fragment of TgAMA-1 (SEQ ID NO:1).

Accordingly, Applicants request withdrawal of the rejection of claim 1 under 35 U.S.C. §102(b) as anticipated by Hehl et al. 1997, Accession number AF010264 and by Hehl et al. 1998, Accession number O15681.

The Examiner rejected claims 1-2 and 23-26 under 35 U.S.C. §102(a) as being anticipated by Hehl et al. 2000, Infection and Immunity, December 2000, p. 7078-7086, Vol 68, No. 12. Applicants respectfully traverse the rejection.

Applicants respectfully submit that the publication date of the Hehl et al reference is December 2000, which is after the date of filing of the application serial No.: 60/247,870. Thus, the Hehl et al., 2000 publication is not considered prior art to the invention as claimed thus obviating the rejection of claims 1-2, and 23-26 under 35 U.S.C. 102(a) as anticipated by Hehl, et al., 2000 reference. Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner rejected claims 1 and 23-25 under 35 U.S.C. §102(a) as being anticipated by Donahue et al. 2000, Molecular Parasitology Meeting, Woods Hole, MA poster Sep, 17-21. Applicants have filed herewith a Declaration of Gary E. Ward, Carolyn G. Conant (nee Donohue), and Brian Ward under 37 C.F.R. §1.132. The Declaration states that the abstract describes Applicants' invention and that the additional authors on the abstract are not co-inventors. Accordingly, Applicants believe the rejections of claims 1 and 23-25 are obviated and request that the Examiner withdraw the rejections.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicants' representative at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Gary E. Ward et al., Applicant

By: _____

MaryDilys S. Anderson, Reg. No.52,560
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2211
Telephone: (617) 720-3500

Docket No. V0139.70050US00
Date: April 13, 2004
x04/18/04x